

Ethical Issues in Pediatric Sham Neurosurgical Trials

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Focus

- I will focus on identifying ethical and regulatory issues raised by possible pediatric sham neurosurgical trials.
- Full evaluation of this topic also would consider issues raised by pediatric research in general, and sham in general.

General Issues

- Pediatric research: waiver of assent, payment, multisite studies, subject's condition requirement.
- Sham: possible deception, therapeutic misconception.

Children

- Children are individuals under 18 years of age who are not able to give their own informed consent.
- Reminder: some individuals under 18 are considered adults for purposes of consent (e.g. mature and emancipated minors).

Parental Permission

- Pediatric research relies on the permission of the child's parents.
- Compared to individual consent, parental permission does not provide the same justification for exposing individuals to risks (e.g. living kidney donation).

Concern

- In addition, enrollment of children cannot be justified by their competent preferences (cf. Alzheimer research).
- Pediatric research thus raises ethical concern.

Concerns Real and Apparent

- The possibility of enrolling children in sham trials raises further concern and likely would be controversial.
- Sham trials pose risks to pediatric subjects by “active” investigators using invasive procedures (these considerations increase public perception concerns).

Acceptable in Principle?

- Given ethical concerns, first need to consider whether it can be acceptable to enroll children in sham intervention trials.
- Assuming pediatric sham trials can be acceptable, would need to determine at what point they should be initiated.

Compelling Justification

- Children should be enrolled in sham trials only when there is compelling reason (default is to exclude children).
- Which reasons are sufficient (disease need; prevalence need; faster trials; lower risk; subject benefit)?

Additional Protections

- The ethical concerns raise the need for additional protections/safeguards.
- The framework for ethical research provides a method to evaluate what protections are needed.

Ethical Principles

- Community Consultation
- Social Value/Scientific Validity
- Fair subject selection
- Acceptable risk-benefit ratio
- Independent review
- Informed permission/assent/dissent

Community Consultation

- The controversial nature of pediatric sham trials suggests the importance of consultation with relevant stakeholders.
- Who should be consulted? What would be a feasible and useful method to obtain input?

Social Value/Scientific Validity

- Sham studies should have high social value which cannot be realized in less risky/invasive ways.
- The requirement of social value highlights the need to evaluate the external, as well as the internal validity of the studies.

Subject Selection

- Subjects should be selected fairly and transparently.
- Scientific considerations should guide subject selection. Also should exclude subjects who would face greater risks.

Risk/Benefit Profile

- Clinical trials must have an acceptable and approvable risk/benefit profile.
- Warning: ensuring this protection for pediatric sham trials involves a multi-step evaluation.

Evaluate Each Arm

- The risk/benefit profile of each intervention should be evaluated (do not just evaluate the study as a whole).
- For example, the US pediatric regulations consider the risks “presented by an intervention or procedure.”

Identify Risks

- Risks of the sham intervention
- Risks of the associated procedures (e.g. anesthesia)
- Risks of any 'nocebo' effects
- Risks of foregoing, at least for a time, any effective treatments

Minimize Risks

- Is a sham necessary: no control?
- Is it possible to blind raters instead?

Less Risky Shams

- When a sham is necessary, use the least risky/invasive sham needed.
- Is an incision needed? Is an incision sufficient?
- Is general anesthesia needed? Does it sometimes reduce risks?

Enhance Benefits

- Using an active control would enhance potential benefits relative to sham.
- Crossover design would allow sham subjects to receive active intervention.

Crossover Design

- Getting the active intervention later may mean fewer risks when more is known.
- But: don't assume that getting the active intervention is always beneficial (i.e. it's research).

Evaluation Risk/Benefit Profile

- Once minimize risks and enhance benefits determine the risk/benefit profile of the active and sham interventions.
- The risk/benefit profile of the active intervention and sham must each be acceptable and also approvable.

U.S. Pediatric Categories

404: Minimal Risk

405: Prospect of Direct Benefit

406: Minor Increase over Minimal Risk

407: Not Otherwise Approvable

Note: The active and sham interventions do not need to be approved in the same risk/benefit category.

Risk Evaluation

- Minimal risk is defined as the level of risk children face in daily life or during routine examinations.
- Reliance on intuition alone is a very unreliable guide for making this determination. Cognitive biases (e.g. familiarity) may be especially influential with respect to invasive shams.

Need for Method

- To implement the minimal risk standard, need to compare the risks of sham to the risks average children face in daily life.
- This requires data on intervention outcomes, data on the risks of daily life, and a method for comparing the two.

One Risk Threshold?

- To protect children, current practice assumes the threshold for minimal risk is the same for all children.
- This approach is important for protecting sick children and children who happen to face greater risks in their daily lives.

Two Risk Standards?

- Increased maturity, unlike sickness and living in a dangerous neighborhood, may justify allowing children to face increased research risks.
- On this approach, greater risks may be allowed in older children who can understand (compared to younger children who cannot understand).

Risk Level

- Sham interventions pose a wide range of risks and invasiveness.
- Some sham interventions involve minimal invasiveness and would seem to pose minimal or minor increase over minimal risk (e.g. sham acupuncture).

Prospect of Direct Benefit

- Many neurological shams are likely to be (judged as) greater than a minor increase over minimal risk.
- Can these shams be approved in category 405: prospect of direct benefit?

Potential Benefit?

- Can placebo effects count as benefits to subjects?
- While this seems possible, one would need data that those who undergo the sham experience some benefit.
- This might require data comparing sham to the natural history of the illness.

One or Two Defaults?

What level of evidence of a placebo effect is needed before:

- Using a sham as the control?
- Categorizing the sham control as prospect of benefit?

Should the evidence standards be the same for the two decisions?

Direct Benefits?

- Assuming placebo effects can count as benefits to subjects, do they qualify as 'direct' benefits?
- The U.S. regulations do not define what constitutes a 'direct' benefit.

Standard Account

- The standard account holds that direct benefits are the benefits of the intervention being tested.
- Any benefits of receiving a sham control would not count as direct.

Proposed Alternative

- Alternative account: direct benefits are the benefits that result from receiving the scientifically necessary procedures.
- Does this account imply that the benefits of receiving sham can qualify as direct? Is this account right?

Prospect of Direct Benefit

- Some chance of direct benefit is not sufficient to approve a study as prospect of direct benefit.
- The potential for direct benefit must justify the risks, and the risk/benefit profile must be at least as favorable as the available alternatives.

Individual Evaluation

- The risk/benefit profiles of clinical trials are evaluated prospectively based on the average expected participant.
- For sham pediatric trials, would evaluation of the risk/benefit profile for *individual* subjects provide additional protection?

Independent Review

- There is a good chance IRBs would refer pediatric sham studies for 407 review.
- What steps can be taken to facilitate and improve the 407 process (for sham trials)?

407 Protections

Would it make sense to adopt 407 provisions for all sham neurosurgical trials with children:

- Public comment prior to study initiation?
- Approval by an expert panel (e.g. to confirm the value of the study)?

Parental Permission

- US regulations require permission of both parents for minor increase over minimal risk research, and for 407 studies.
- Should the permission of both parents when available be required for all pediatric sham trials?

Assent

- AAP recommends 7 as the age of assent. This may be too low. However: is lower better for more controversial studies?
- Should enrollment be limited to children who exceed the age threshold for assent, or to children found able to assent?

Possible Added Protections

Possible enhancements to the process of obtaining parental permission and assent:

- Require assessment to ensure that the parents (children) understand the trial?
- Use independent consent/assent monitors?

Dissent

- The U.S. federal regulations do not include a dissent requirement.
- If a sham trial were open to children who cannot assent, respect for their sustained dissent should be mandated.

Conclusion

- Possible pediatric sham trials raise important ethical and regulatory issues, and are likely to be controversial.
- If such trials are considered, it will be important to prospectively identify and address the ethical, regulatory and public perception issues.